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Predictive value of ultrasound scoring in relation to clinical and histological parameters in xerostomia patients

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Abstract

Background:

Salivary gland dysfunction is one of the main clinical features of SS, manifested by xerostomia with subsequent complications and well-established effects on the person's quality of life.

Objectives:

To determine firstly whether selected tests of salivary gland function and structure; unstimulated whole salivary flow rate (UWSFR), parotid flow rate (PFR), clinical oral dryness score (CODS) and ultrasound score (USS), can discriminate SS from non-SS sicca patients and secondly whether these tests can differentiate between patients in different subgroups of SS.

Method:

UWSFR, PFR, CODS and USS were determined in 244 patients comprised of SS patients (n=118), SS patients at higher risk of lymphoma (n=30) or with lymphoma (n=26), and non-SS sicca disease controls (n=70).

Results:

All assessments showed a significant difference between the overall SS group and the disease control group, attributed mainly to the lymphoma subgroups of SS ($p<0.0001$ for all parameters). There was a significant correlation (spearman r= 0.7, p value <0.0001) and 87.3% agreement between USS and the histology focus scores of 119 patients.

Conclusion:

The results suggest that salivary gland tests including USS can aid in differentiating between SS and non- SS dry mouth, especially the subgroups of SS with lymphoma or at higher risk of developing lymphoma.

Introduction

Sjögren’s syndrome (SS) is a heterogeneous multi-systemic disease diagnosed by certain criteria requiring multiple clinical and laboratory parameters (Shiboski et al., 2017). Xerostomia is one of the main clinical manifestations seen in SS patients. However, this subjective complaint may not be necessarily reflecting an actual hyposalivation and loss of salivary gland function (Billings et al., 2016). The loss of glandular function can be measured via overall or specific glandular flow rates, by assessing dryness using the clinical oral dryness score (CODS) or implied from assessing functional glandular structure using the ultrasound severity score (USS).

SS is accompanied by changes in salivary gland structure including focal lymphocytic infiltration and loss of secretory tissue. Histological assessment of gland biopsies is frequently used to demonstrate the loss of normal tissue that may result in functional loss. Such histological changes are semi-quantitatively assessed using a focus score (≥1 lymphocytic aggregate of ≥50 cells per 4 mm^2) (Chisholm & Mason, 1968; Daniels et al., 2011). However, functional impairment might not always result of tissue loss and patients with normal glands might manifest signs of functional loss (Colella, Cannavale, Vicidomini, & Itro, 2010). Thus, in this study it was decided to assess easily applied tests such as flow rates and dry mouth score while correlating selected measures (USS) with histology.

Due to its well- known detrimental effect on the person’s quality of life (Niklander et al., 2017) , monitoring xerostomia is of major importance. Indeed, salivary gland assessments are routinely used as part of the objective diagnostic criteria of SS, specifically unstimulated whole flow rate (UWSFR) with a cut- off of 0.1 ml/min (Shiboski et al., 2017). In addition, individual glandular flow rate tests may demonstrate the extent of involvement of a particular gland. Even though submandibular/sublingual flow rates might be useful in the early phases of SS, parotid flow rate (PFR) might be more informative in patients with longer (progressive) disease duration according to Pijpe et al., (2007). Scoring systems have been used to monitor oral dryness and one such system is The Challacombe scale or Clinical Oral Dryness Score (CODS), which uses a simple numeric system enabling semi-quantification of the severity of oral dryness over time (Challacombe, Osailan, & Proctor, 2015). Salivary gland structural changes can also be evaluated using ultrasonography, which despite not being part of the diagnostic criteria, has been suggested as a diagnostic instrument in SS in a number of studies (Astorri et al., 2016; Jousse-Joulin et al., 2016, Ali et al, 2013). A simplified ultrasound scoring system (USS) was developed (Brown, 2010), based on a system proposed by Hočevar et al., (2005). USS may be uninformative in early phases of SS, but might be that more specific in later stages with higher US scores.

This retrospective study has assessed the ability of some easily applied and repeatable salivary gland parameters to differentiate between SS subgroups and another non- SS sicca group. SS groups included SS, SS at higher risk of developing MALT-L and those who had developed MALT-L. As the differentiation between the more severe groups could allow for treatment at the first signs of cancer and improve the likelihood of success. Comparison was made with a disease control (DCT) group consisting of patients with non- specific sialadenitis, nodal osteoarthritis & xerostomia (SNOX) (Kassimos et al., 1997), patients with xerostomia and on polypharmacy therapy and those without a specific diagnosis (not otherwise specified; NOS). We hypothesised that measurements of salivary gland involvement; whole mouth and parotid flow rates, CODS and USS may discriminate between SS subgroups and other dry mouth patients. A secondary hypothesis was that USS of major salivary glands reflects salivary gland damage in all glands and would significantly correlate with minor salivary glands histopathology focus scores (Ali et al 2013).

Materials and methods

Study group

The protocol for this study was reviewed and approved by the National Research Ethics Service (NRES) Committee (11/LO/1121). Patients with symptomatic dry mouth attending Guy's and St. Thomas's Hospital Oral Medicine department (GSTT NHS Foundation Trust) were included. The series of 244 was divided into 2 groups:

a) Disease control subjects (DCT; n= 70) subgrouped according to their relevant findings:
   1) Patients who complained of xerostomia and were on polypharmacy therapy with a reduction of UWSFR as described by Wolff et al. (2017) (n=25).
   2) Patients complaining from xerostomia with a negative serology test for SS while having non-specific sialadenitis on their biopsy results and confirmed generalised nodal osteoarthritis were diagnosed as SNOX (n=25) (Kassimos et al., 1997).
   3) Not otherwise specified (NOS; n=20) patients who did not fit any of the above groups.

b) Overall SS group (n=174) was subdivided into:
   1) Patients who fulfilled the American-European Consensus Group (AECG) criteria (Vitali et al., 2002) as SS patients (n=118) without risk factors or the presence of MALT lymphomas (SS-low risk).
   2) Patients defined as higher risk of developing MALT-L (n=30) presenting with at least three of any of the commonly reported risk factors (e.g. persistent or recurrent parotid enlargement, cryoglobulinemic vasculitis, raised β2 microglobulin levels, lymphopenia, hypergammaglobulinemia, hypocomplementemia, high focus score, germinal centre in their biopsy and previous lymphoma) (Nocturne & Mariette, 2015). In order to have more stringent selection of specified patients who were considered at higher risk of MALT lymphoma development, a group of at least 3 factors was chosen as selection criteria.

3) SS with (MALT-L) patients (n=26). MALT lymphoma was confirmed via histopathological assessment of biopsies of either parotid glands in most of the patients or minor salivary glands in 2 patients, while one patient had submandibular lymphoma.

The mean time for development of lymphoma after the diagnosis of SS was found to be about 4 years. Treatment had been commenced within the same year of MALT-L diagnosis and was surgical excision (partial or full) for 13/26 patients (50%) followed by chemotherapy or radiotherapy in some cases. For the other 13 patients a watch and wait policy (observation) was adopted for 6 (23%) patients, three patients (13%) had radiotherapy (4 Gy in two fractions) (low intensity radiation) while three had chemotherapy (10 mg chlorambucil cycles). One patient had rituximab treatment. Salivary measurements were recorded after their treatment.

Data collection

Electronic patient records (EPR) and medical notes of patients were initially examined during the years of 2013 to early 2016. All patients had been or were currently being followed at clinics. Whole and parotid saliva flow rates, ultrasound and dry mouth scores (USS and CODS) were recorded for all the patients when present in the medical notes. In addition, blood tests indicating the increased risk of developing lymphoma were recorded (e.g. complement level, cryoglobulins, gammaglobulins and β2 microglobulin levels). Cross-sectional comparisons between different subgroups were made. A summary of the different diagnostic groups for the cross-sectional study is shown in Table S1 and a detailed protocol of each test are provided (supplementary material, Figures S1-4).

Data analysis

The sample size was calculated using independent samples t test. Assuming a moderate effect size of 0.4, a study with 80% power would require a total sample of 244 (70 for the Disease control group and 174 for the Overall SS group) with an allocation ratio of 0.4 to test the difference in parameters between the groups at 5% level of significance. The power calculation for this study was carried out using Gpower version 3.1.5. For the cross- sectional analysis, comparison between 2 groups (disease controls vs. overall SS groups) was made via Mann–Whitney U tests then Kruskal-Wallis test followed by Dunn's post-hoc tests to determine the differences between the multiple groups (SS subdivisions) for parameters that were not normally distributed (PFR, UWSFR and USS). CODS were normally distributed thus one- way ANOVA followed by Scheffe post-hoc test were used for multiple comparisons and independent sample t- tests for comparing 2 groups (disease controls vs. all SS groups). Spearman's rank correlation coefficient (Spearman's rho) was used to determine the associations between flow rates and scores. Cohen's kappa coefficient was used to measure the level of agreement between biopsy focus scores and USS while Spearman's rank correlation coefficient (Spearman's rho) was used to assess their relationship. Discriminant validity was assessed via Receiver Operator Characteristic (ROC) curves to determine the ability of USS to differentiate between SS subgroups and the DCT group. Negative and positive predictive values as well as odds ratios were calculated from contingency table generated using the optimal cut-off. The median and quartiles were used as estimates of central tendency and dispersion of non-parametric data while means and standard error of mean (SEM) were used to demonstrate the parametric data. The significance level was set to $p<0.05$.

Results

Clinical parameters outcome

UWSFR

The overall median (Q1-Q3) UWSFR for the SS group as a whole group was 0.04 (0- 0.16) ml/min which was significantly reduced when compared with the disease control group 0.12 (0.1- 0.24) ml/min ($p < 0.0001$). (Fig.1 (A), (a)).

Subgrouping of SS revealed a reduction of flow rates of the MALT-L higher risk group 0.01 (0- 0.1) ml/min and MALT-L group 0.002 (0- 0.06) ml/min when compared with the disease control group ($p < 0.0001$ for both) and the SS-low risk subgroup 0.08 (0- 0.24) ml/min ($p=0.039$ and 0.049 respectively) (Fig.1 (A), (b)). No significant difference was detected between the SS-low risk subgroup and disease control group (Fig.1 (A), (b)).

Stimulated PFR

The (median (Q1-Q3)) stimulated PFR of the overall SS group (0.14 (0- 0.3)) ml/min was significantly lower than the disease control group 0.28 (0.16- 0.44) ml/min ($p < 0.0001$) (Fig.1 (B), (a)). In the SS subgroups, MALT-L higher risk 0.01 (0- 0.25) ml/min and MALT- L 0 (0-0.13) ml/min were significantly less when compared with disease control group ($p=0.005$ and <0.0001 respectively) whereas only the MALT-L group was reduced compared with the SS-low risk subgroup 0.22 (0- 0.33) ml/min ($p=0.022$) Fig.1 (B), (b)). The mean PFR in the SS-low risk subgroup was not reduced in comparison with the disease control group (Fig.1 (B), (b)).

USS

The median (Q1-Q3) USS of the overall SS group of 5 (4-7) was significantly greater than the disease control group 0 (0-0) ($p < 0.0001$) (Fig.1 (C), (a)).

All SS subgroups showed significantly increased median values when compared with disease controls ($p < 0.0001$ in all) (Fig.1 (C); SS 5 (3-5), MALT-L higher risk 6.5 (5-8) and MALT-L 7.5 (6-9) (b)). In addition, both mean values in the MALT-L higher risk and MALT-L groups were significantly increased when compared with the SS-low risk subgroup ($p= 0.001$ and $p < 0.0001$ respectively) (Fig.1 (C), (b)).

CODS

The mean dry mouth score (CODS) of the overall SS group (mean± SEM) (4.9± 0.2) was significantly greater than the disease control group (DCT) (3.2± 0.3) ($p< 0.0001$) Fig.2 (a). Significantly higher mean USS values in all SS subgroups were observed compared with (DCT); SS-low risk (4.5± 0.3), MALT-L at higher risk (5.3± 0.4) and MALT-L (6.5± 0.5) ($p=0.013$, 0.005 and <0.0001 respectively). Amongst the subgroups, the mean CODS of the MALT-L group was significantly higher than the SS-low risk subgroup ($p=0.008$) (Fig.2 (b)). All the SS salivary gland disease measures (clinical parameters) correlated well with each other in the overall series (n=244), notably UWSFR with stimulated PFR (strong correlation $p<0.001$) and CODS. CODS moderately correlated with both flow rates. Ultrasound scores showed a weak but statistically significant correlation with all the measures as shown in Table 1.

Association of USS with focus scores

The histopathology focus scores of 119 labial gland biopsies out of the 244 subjects were available (62 SS and 57 DCT subjects). Of the 62 SS patients, 43 patients were in the SS-low risk subgroup with a mean score ± SEM of 3.7± 0.04, 11 were MALT-L higher risk patients with a mean score of 5.2± 0.6 and 8 were MALT-L patients with a mean score of 6.6± 0.6. The mean focal scores for 57/70 DCT patients was 0 and their histopathology results indicated either normal gland or non-specific sialadenitis. Biopsies were not undertaken for the rest of the controls while the remaining SS patients fulfilled the criteria for SS but their biopsies had not been scored. A highly statistically significant positive correlation was noted between the USS and focus score of the overall group (spearman $r= 0.7$, n=119, $p <0.0001$). The correlation in the overall SS group was also statistically significant (spearman $r=0.3$, n=62, $p <0.0001$).

Measurement of agreement

An ultrasound score of ≥4 was considered positive for SS patients and was used to sort them accordingly to positive and negative disease groups. The focus score of ≥ 1 per 4 mm^2 was considered positive for SS. Cohen's kappa (κ) showed a good agreement between both methods, $\kappa = 0.748 \pm$ (SEM) 0.061, $p < .0001$. The overall agreement was calculated as 87.3% and the USS results had a positive predictive value (PPV) of 88.1% and a NPV of 89.6% of the biopsy results; out of the 60 patients with negative biopsy results, 8 were positive for ultrasound while out of the 59 patients with positive biopsy results, 7 were negative for ultrasound.

Optimal cut- off of ultrasound score

From the optimal cut-off points that were computed based on optimum separation via the ROC curve, USS ≥4 was selected providing the highest sensitivity of 81.0% (95% CI: 74.4- 86.6) and specificity of 94.3% specificity (95% CI: 86.0- 98.4).and. The Area Under the Curve (AUC) was 0.92 (95%CI; 0.89 to 0.96) and $p<0.0001$ with a likelihood ratio of 7.54 (Fig.3). The USS cut-off of 4 was used to generate a 2X2 contingency table in order to estimate the PPV, negative predictive value (NPV) and odds ratio where chi square tests were used (Table 2).

Discussion

This study has found that the USS may not only discriminate between SS and non-SS dry mouth patients, but also between SS MALT-L related groups (at higher risk and with MALT-L) and SS non-MALT-L groups. It was decided to select tests that can be repeatedly and easily applied and to correlate the selected measures with histology. A group of patients with non-specific sialadenitis, primary generalised nodal osteoarthritis & xerostomia (SNOX) were enrolled as part of a non-SS sicca (disease) control group because the disease is often confused with SS and shares some symptoms including fatigue, dryness complaints and signs as well as inflammation of the salivary glands (non-specific vs. focal in SS groups). SNOX has been little tested by other studies since its first description by Kassimos et al., (1997) and later by Price and Venables, (2002) and is probably underdiagnosed, thus it was interesting to follow this disease group further. Regarding the patients at higher risk of MALT-L, a number of risk factors have been documented from large cohort studies (Nishishinya et al., 2015; Papageorgiou, Voulgarelis, & Tzioufas, 2015). However, there is no clear explanation as to why these factors should facilitate lymphoma development but, it might be that they are features of a more advanced disease. The presence of Ro/SS-A antibodies is correlated with longevity since onset of SS, greater damage of the glands and extra-glandular manifestations which can be one of the predictors of lymphoma development.(Maslinska, Przygodzka, Kwiatkowska, & Sikorska-Siudek, 2015). Although in this study all of the subjects in the higher risk of MALT-L and confirmed MALT-L groups were female, there appears to be no published evidence demonstrating a gender difference probably due to the predominance of female patients in SS (Nishishinya et al., 2015). One study has suggested that male-sex was not associated with lymphoma development (Nishishinya et al., 2015).

In this study, we took the opportunity of defining a group of patients with a higher risk of developing maltomas by having at least three risk factors (Nocturne & Mariette, 2015) and comparing their clinical parameters with low risk SS patients and those SS who had already developed MALT lymphoma. To our knowledge this is the first study to report discrimination between subgroups of patients with lymphoma (MALT-L) or a higher risk of developing MALT-L from SS non MALT-L using an ultrasound score, although such an application has previously been suggested

(Bootsma, Spijkervet, Kroese, & Vissink, 2013). Such discrimination was not found between both MALT-L related SS groups (at higher risk and with MALT-L). The median ultrasound scores also showed differences between all groups of SS patients and disease controls, which included patients with SNOX, a non-specific salivary gland chronic inflammatory disease accompanied by dry mouth. Using a cut-off of USS ≥ 4 yielded 81.03% sensitivity, a specificity of 94.3% and odds ratio of 70.5% when comparing all SS patients with disease controls. The use of USS as a diagnostic test has previously been suggested by two systematic reviews, which reported comparable results. Delli et al., (2015) stated a pooled sensitivity of 69% (95%CI: 0.67–0.71), specificity of 92% (95%CI: 0.91–0.93), and diagnostic odds ratio of 33.89 (95%CI: 20.75–55.35) in their meta- analysis, suggesting that USS could be efficacious in identifying patients with SS, although the lower sensitivity indicates a considerable number of false negatives who may be patients at their early stages of SS. Another systematic review by Jousse-Joulin et al., (2016) included studies evaluating the usefulness of ultrasound and found a range of sensitivity (45.8 to 91.6%) and specificity (73 to 98.1%).

A highly significant correlation between ultrasound scores and histology focus scores of all SS subjects was found in the present study (spearman r=0.7, p value <0.0001) suggesting that lymphocytic infiltration is influencing USS and the latter can be used at all stages of SS. It would therefore be appropriate to use ultrasound as a first measure in SS as suggested previously (Jousse-Joulin et al., 2016). In theory, a positive result for USS (4 or more) complemented by other tests such as ocular, serology and salivary flow rates could thus replace the need for performing a labial gland biopsy as suggested by Takagi et al. (2014) where USS was reported to be used as alternative to any of the 3 criteria of the American College of Rheumatology (Shiboski et al., 2017). Recently Astorri et al., (2016) also confirmed the potential of ultrasound in diagnosing SS, reporting an agreement of 91% (κ=0.82) with histological focus score and a positive predictive value of 85% and a negative predicative value of 96%. In our results, the level of agreement was lower showing 87.3% concordance between USS and focus score with a slightly higher (88.1%) positive predictive value but lower negative predictive value (89.6%). These levels of agreement occur even though the focus score in our study analyses minor salivary glands whilst ultrasound assesses major salivary glands. The predictive values in the present study were calculated based on confirmed diagnoses and there was a lower negative predictive value (66%) while the positive predictive value was higher (97%) than the values calculated in relation to histology results. Some studies have suggested adding USS to the objective measures which form the criteria for SS diagnosis since they showed an increased sensitivity of up to 87% while retaining specificity (Cornec et al., 2013). However, there is a need firstly to determine if other conditions such as viral or bacterial infections give a similar ultrasound picture and secondly develop a consensual scoring system for ultrasound with consistent procedures and appropriate training in achieving reproducible results (Jousse-Joulin et al., 2016). Also, we also noted that some patients possibly in earlier stages of SS with US score of 3 or less were considered as negatives for USS but who satisfied the ACR criteria having positive histology results and reduced flow rates.

Unsurprisingly there was a significant reduction in the mean UWSFR in the overall SS group when compared with the disease control group. The reduction is mostly attributed to the subgroups of MALT-L higher risk and MALT-L, which showed the greatest reductions. Whole flow rate could not differentiate between SS-low risk subgroup and the other causes of dryness and this is supported by a number of studies (Billings et al., 2016; Ohyama et al., 2015; S. M. Osailan, Pramanik, Shirlaw, Proctor, & Challacombe, 2012; van den Berg, Pijpe, & Vissink, 2007). There were similar findings for PFR, which was reduced in the overall SS patients in comparison to the disease controls and this was mainly attributable to the MALT-L higher risk and MALT-L subgroups since no differences were found between the SS-low risk subgroup and disease controls as have been reported previously (Kalk et al., 2001; Kalk, Vissink, et al., 2002; S. M. Osailan et al., 2012; van den Berg et al., 2007). The median value of PFR in the MALT-L group was reduced compared with the SS-low risk subgroup. UWSFR and PFR showed a strong correlation ($r=0.6$, $p<0.0001$) in concordance to Kalk et al., (2002) and Vissink et al., (2003) ($r=0.75$, $p<0.001$). However, it appears that parotid gland involvement is more evident in later stages of SS when there may be little correlation between whole mouth and parotid flow rates. The reduction of whole saliva has been attributed to the significant decrease in the submandibular/sublingual flows at early stages (Kalk et al., 2001; Kalk, Vissink, et al., 2002; Pijpe et al., 2007; van den Berg et al., 2007; Vissink et al., 1993).

With regards to CODS, the mean value of the overall SS group was greater than the disease control group and the mean CODS value in each of the subgroups were also higher than the disease control group. Values in the MALT-L group was significantly greater than the SS-low risk subgroup. Osailan et al., (2012) previously reported an increased CODS of SS patients when compared with SNOX and NOS (Challacombe et al., 2015). The significant change seen in the MALT lymphoma group might also be affected by treatment, whether it was chemotherapy or surgery. Cross-sectional association identified a strong negative correlation between CODS and salivary flow rates (either whole or parotid). Other studies have identified similar findings of an inverse relationship between CODS and salivary flow rates (irrespective of their diagnosis) (Challacombe et al., 2015; S. Osailan, Pramanik, Shirodaria, Challacombe, & Proctor, 2011; S. M. Osailan et al., 2012). The results of this study suggest that SS patients at risk of developing MALT lymphomas have significantly different values of specific salivary parameters (WFR, PFR, CODS and USS) from SS and non- SS sicca patients. Longitudinal studies may confirm the combination as useful markers for assessing lymphoma risk in SS. However, further analyses of the variations in the parameters (UWSFR, PFR, CODS and USS) assessed in this study are necessary and the inter- and intra- individual and observer variability should be considered in order to determine whether the differences observed are the result of variations in the examination technique or real individual variations.

Conclusions

SS patients with or at higher risk of developing MALT lymphomas have significantly different values of specific salivary parameters (WFR, PFR, CODS and USS) from SS and non-SS dry mouth patients. USS would be the ideal non-invasive test to differentiate and monitor SS patients in general (81% sensitivity and 94% specificity) since USS can be easily repeated and might be used in place of sialography to reveal structural change in salivary glands. USS showed a good correlation and agreement with focus scores. An optimum cut- off ultrasound score of 4 could differentiate SS from non- SS patients. This can be used to prioritise biopsy for patients showing evidence of SS in their ultrasound. Ultrasound scores and CODS were higher in the two advanced SS groups (at higher risk of MALT-L and confirmed MALT-L) and can be used to monitor development of MALT-L.

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Fig. 1. Unstimulated *whole mouth salivary flow rates (a), parotid flow rate (b), and ultrasound score (USS) (c) of different groups n= (244).*
(A) SS groups are combined and (B) SS subgroups.
DCT; disease controls which are not otherwise specified (NOS), sialadenitis, nodal osteoarthritis & xerostomia (SNOX) and patients complaining of xerostomia while on polypharmacy therapy, SS; Sjögren's syndrome, MALT-L; mucosa associated lymphoid tissue lymphoma, SS at risk; SS at higher risk of MALT-L. Data are reported as median ± (IQR) and expressed as mL/min.
(A) Mann–Whitney U test (B) Kruskal-Wallis test followed by Dunn's post hoc test.

Fig. 2. *Clinical oral dryness score (CODS) of different groups n= (244).*
(A) SS groups are combined (B) SS subgroups.
DCT; disease controls which are not otherwise specified (NOS), sialadenitis, nodal osteoarthritis & xerostomia (SNOX) and patients complaining of xerostomia while on polypharmacy therapy, SS; Sjögren's syndrome, MALT-L; mucosa associated lymphoid tissue lymphoma, SS at risk; SS at higher risk of MALT-L. Data are reported as mean ± (SEM).
(A) Independent t- test (B) One way ANOVA followed by Scheffe post hoc test.

Fig. 3. *ROC curve of ultrasound score in identifying patients with Sjögren's syndrome.*
Overall SS (n=174) and non-SS (disease controls) (n=70) total (n=244).

Table 1. *Spearman correlation of the clinical parameters (whole flow rate, parotid flow rate, ultrasound score and clinical oral dryness score*

Spearman's rho				
	UWSFR	**PFR**	**USS**	**CODS**
UWSFR	1			
PFR	.604**	1		
USS	-.39**	-.37**	1	
CODS	-.59**	-.503**	.39**	1

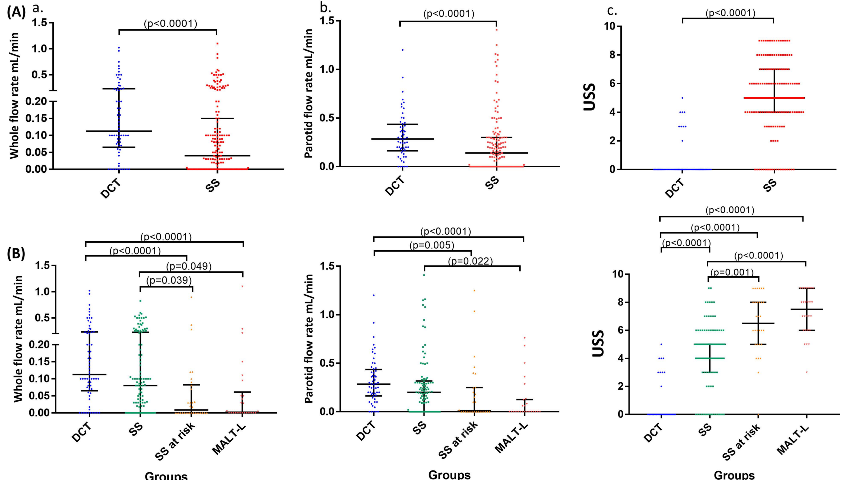
*UWSFR; unstimulated whole saliva flow rate, PFR; parotid flow rate, USS; ultrasound score, CODS; clinical oral dryness score. ** p<0.0001. Correlation is significant at the 0.01 level (2-tailed)*

Cut-off (4)	Overall Sjögren's syndrome	Disease controls	Total
USS + (> OR =4)	(True positives) 141	(False positives) 4	145
USS - (<4)	(False negatives) 33	(True negatives) 66	99
Total	174	70	244

Table 2. X^2 *analysis of 244 patients with symptomatic dry mouth*

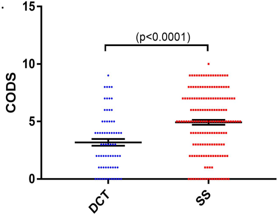
(Chi square=10.84; p<0.0001) *PPV=97.24% (95%CI; 93.12- 98.92)*

Odds ratio= 70.5% (95%CI; 24.16- 187.3) *NPV=66.67% (95%CI; 56.91- 75.18)*

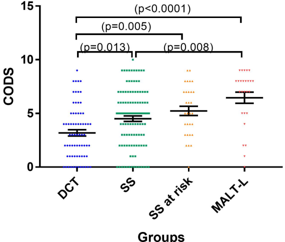


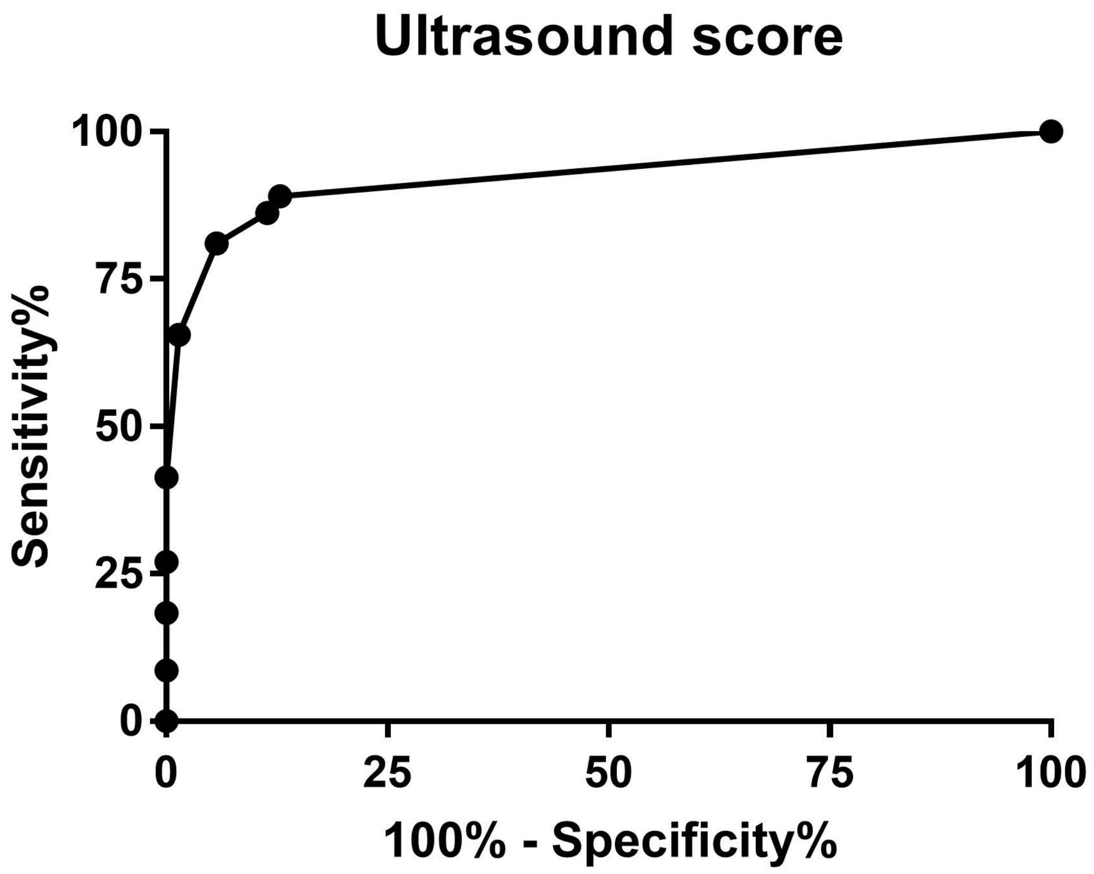
(A)
a.
b.
c.
(p<0.0001)
Whole flow rate mL/min
Parotid flow rate mL/min
USS
DCT
SS
(B)
(p=0.049)
(p=0.039)
(p=0.005)
(p=0.022)
(p=0.001)
SS at risk
MALT-L
Groups

a.


15
10
5
0
CODS
(p<0.0001)
DCT
SS

b.


15
10
5
0
CODS
(p<0.0001)
(p=0.005)
(p=0.013)
(p=0.008)
DCT
SS
SS at risk
MALT-L
Groups


Ultrasound score
100
75
50
25
0
Sensitivity%
0
25
50
75
100
100% - Specificity%